INTEGRA LIFESCIENCES

A New Bioabsorbable Polymer: An Ideal Material for Medical Implants?

For more than 100 years, orthopedic surgeons have been repairing serious bone fractures by binding the fractures with screws, pins, and other fixation-type devices. Early on, these devices were often made from common metals such as iron or steel. Later on, they were made of highly sophisticated metal alloys of titanium, zirconium, niobium, and tantalum. Still the search continued for materials that would be more compatible with the human body, and that search led researchers to consider bioabsorbable polymers.

COMPOSITE PERFORMANCE SCORE
(based on a four star rating)
* * * *

Problems with Existing Materials

While effective in binding the fractured bone, the devices made of common metal corroded when they were implanted in the body and released toxins that could cause inflammation, infection, and even life-threatening injury to the patient. The metal alloys offer major improvements because they do not corrode when exposed to body fluids and therefore can be left inside the body for long periods of time without releasing harmful toxins. They, too, however, have serious drawbacks. Metal alloys are much harder and stiffer than the bone they replace or support, and can interfere with the regrowth of the bone.

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Many patients with metal alloy implants must under-go follow-up surgery, with its associated cost, risk, and trauma, to remove the implant once the healing process has occurred. According to a recent study, the cost of a second surgery can range from $850 for devices located in the shoulder to $2,200 for devices located in the knee. More than 34,000 of these follow-up surgeries are performed in the United States each year, resulting in costs of $30–75 million.[1]

Bioabsorbable Polymers Offered Promise—and Potentially Dangerous Toxins

Polymers offer great potential as a substitute for alloys for use in orthopedic implant devices. Polymers can be made to be biocompatible and designed to exhibit more bone-like properties. Their mechanical properties can be strong enough to withstand weight-bearing applications, yet they still retain a degree of elasticity not available with metal alloys. Most important, polymers can be made to be bioabsorbable, that is, they can be made to dissolve and slowly be absorbed by the body. Further, the rate of dissolving can be engineered so that it is consistent with the rate of new bone growth. Under ideal conditions, a bioabsorbable polymer could encourage bone healing while the body slowly metabolizes it. This eliminates the need for a second surgery that may be required when an unyielding metal alloy is implanted.

A serious problem existed, however, with available bioabsorbable polymers—polylactic acid, polyglycolic acid, and polydioxanone. When they dissolve or degrade inside the body, they tend to release acids and other toxins that are harmful. For sutures and small

1 A Framework for Estimating the National Economic Benefits of ATP Funding of Medical Technologies, " The Research Triangle Institute Center for Economics Research, Project number 6715-01 FR, NIST GCR 97-737, April 1998, section 3.

staple devices this is not a serious problem because the quantity of harmful substances released is small. But for larger devices, such as weight-bearing screws, the release of harmful products can be significant and can cause inflammation problems, similar to the problems that occurred with the crude metal devices of the past.

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Over the past two decades, scientists have attempted to reengineer these polymers to minimize the release of harmful substances and reduce the resulting inflammation. This research has had some success but apprehensions remain over problems of bio-incompatibility. Market experts suggest that unless a major breakthrough occurs that solves this problem, the market for bioabsorbable polymer implants will not fully develop and patients will have to continue to undergo secondary surgeries with their associated costs and risks.

ATP Funds Research for an Improved, Toxin-free Bioabsorbable Polymer

In the early 1990s, Dr. Joachim Kohn, a professor of chemistry at Rutgers University, invented new "pseudo-polyamino acids" based on tyrosine, a naturally occurring amino acid. The polymer's physical properties are similar to existing, FDA-approved bioabsorbable polymers, but because it is derived from tyrosine, any acids or toxins it releases are done so at significantly slower rates.

Several implant device manufacturers showed an early interest in Dr. Kohn's invention, but none were willing to make a commitment to develop the material because the technical risk of doing so was very high.

Development of the polymer required the creation of a manufacturing process that guaranteed the material's purity and uniform characteristics on an industrial scale. In addition, quantities of the new polymer had to undergo a series of rigorous tests to show that the material was indeed capable of being used safely and effectively in implant devices. All of this had to be accomplished before additional funds would be committed to run the additional clinical trials mandated by the FDA approval process.

Integra LifeSciences Corporation, a small biomaterials company in New Jersey, approached Dr. Kohn with a plan to accelerate the development of this new polymer. Integra, in research led by Dr. George L. Brode (principal investigator for the ATP project) and Dr. John Kemnitzer, would develop a scaleable manufacturing process for the tyrosine polycarbonate and then perform tests to assess the new material's potential for use in implant devices. Once the difficult technical problems were overcome and the polymer's potential was demonstrated, it was expected that private investors in the new implant technology could be attracted.

To offset the high technical risks of this endeavor, Integra submitted a single-company proposal to the Advanced Technology Program's 1993 General Competi-tion. Potential economic benefits looked strong, the research plan solid, and Integra received a $2 million, three-year award from the ATP that began in January 1994.

Integra Overcomes Technical Obstacles

The first major task of the project was to design and develop a scaleable process technology that allows for flexible control of several key physical properties during manufacturing and ensures that the polymer can be produced with a high degree of purity. This work led to the development of the successful "Biphasic Process." Integra filed a patent on this process, and showed that it was capable of producing commercial quantities of the new polymer. Having developed the manufacturing

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process technology, Integra's next task was to assess the physical properties of the new material and prepare prototype devices for in vitro and in vivo testing. Working with Rutgers University and New York's Hospital for Joint Diseases, Integra conducted a series of tests to study how well the new polymer material interacts with living cells. Toxicity and sensitization studies were performed to assess such issues as tissuecompatibility, inflammatory response, bone growth, and hard tissue response. The results confirmed that the new polymer does not emit toxic by-products when it degrades and does not have an adverse affect on tissue or bone. Other tests evaluated the polymer's resorption properties, i.e., how the process of bone re-growth interacts with the degrading

PROJECT HIGHLIGHTS

Project:
To develop a new polymer material for making implantable surgical devices such as screws, plates, pins, wedges, and nails for repairing fractured bones; to design and develop a scaleable process for making it; and to assess the polymer's suitability as an effective implant material.

Duration: 1/1/94 – 12/31/96
ATP Number: 93-01-0085
Funding (in thousands):

ATP	$1,999	81%
Company	467	19%
Total	$2,466	

Accomplishments:
Development of a new class of bioabsorbable polymers based on tyrosine, a naturally occurring amino acid, was greatly accelerated. This new polymer can be used to create implants for surgical devices, such as pins and screws for repairing fractured bones. Implants made from this polymer do not exhibit the problems of brittleness, release of toxins on absorption, or the need for surgical removal– all characteristics of implants made with existing materials. The material and process for making it were brought to the stage where prototype devices could be produced for testing and demonstration, and commercial development partners, in collaboration with Integra LifeSciences Corporation, could file for FDA approval. The project's accomplishments include:

- development of a process to produce commercial quantities of tyrosine-based polymers, for which Integra filed a patent in 1997;

- synthesis and characterization of bioabsorbable tyrosine polycarbonates and creation of a variety of prototype fixation devices;

- evaluation of the bioabsorbable polymer through studies of toxicity and sensitization, which indicate that the new polymer is comparable to existing biopolymers in terms of its mechanical and resorption properties, and superior in terms of its biocompatible properties;

- diffusion of new technical knowledge through numerous presentations and 15 publications;

- licensing of the technology to two commercial partners; and

- recognition of the technology by the New Jersey Research and Development Council who presented the Thomas Alvin Edison Award to Dr. Kohn of Rutgers University for project-related research.

Commercialization Status:
On September 18, 1998, Integra announced that it had formed two strategic commercial alliances for the commercial development of its tyrosine-based polymer. An alliance with Bionx Corporation is pursuing use of the new polymer to develop surgical screws, plates, pins, wedges, and nails to be used for the fixation or alignment of musculoskeletal fractures. An alliance with Linvatec, a subsidiary of CONMED Corporation, is pursuing use of the polymer to develop arthroscopic fixation devices such as surgical screws, tacks, and other anchoring devices to attach soft tissue to bone in the knee and shoulder. The partners have filed with the FDA for approval, and forecast their first products will be launched shortly after approval.

Outlook:
The tyrosine-based polymer technology is a platform technology with broad applications in orthopedics (fracture fixation), cartilage and ligament repair, wound care, cardiovascular repair, drug delivery, and other uses. In the near term, economic benefits are expected to accrue from the development of a wide range of orthopedic fixation devices by Integra and its established commercial partners. The outlook for continued development and commercialization of the technology is excellent.

Composite Performance Score: * * * *

Number of Employees: at project start 32; number of employees at project end: 129

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polymer. Although the tests were not yet complete at the time of this study, early results suggest that the new polymer has resorption rates similar to existing FDA-approved polymers, but does not cause the adverse secondary reactions due to release of harmful materials.

The polymer's mechanical properties were tested and optimized. The results of these tests indicate that the new polymer can be used in a number of orthopedic devices, including weight-bearing devices such as large surgical screws. Integra is also evaluating various composite materials that could be used with the new polymer to produce materials with a wide range of physical and mechanical properties. Additional patent applications in this area are also planned.

Integra's new commercial partners have agreed to undertake and fund the studies necessary for FDA approval, a commitment neither Bionx nor Linvatec would have made were it not for the accomplishments of the ATP project.

Integra forms alliances with Bionx and Linvatec

With ATP's support, Integra and Dr. Kohn successfully accelerated the development of this new polymer to the point that implant device manufacturers could evaluate the risk associated with commercialization. Two years after completion of the project, Integra formed two strategic commercial alliances committed to the development of new orthopedic implant devices using the new material.

Integra formed an alliance with Bionx Corporation to develop surgical screws, plates, pins, wedges, and nails for the fixation and alignment of fractures and for other musculoskeletal surgical applications. An alliance with Linvatec, a subsidiary of CONMED Corporation, will develop smaller screws, tacks, and other arthroscopic fixation devices that will be used to attach soft tissue to bone in the knee and shoulder. In each case, Integra's new commercial partners have agreed to undertake and fund the studies necessary for FDA approval, a commitment neither Bionx nor Linvatec would have made were it not for the accomplishments of the ATP project. Both partners expressed the expectation that their first products would be launched soon, but the various filings and approvals through the Food and Drug Administration take time, and it is difficult to predict timing with accuracy.

According to Dr. Brode, "without ATP, I don't know that we could have proceeded. We would be at least five years or more behind where we are."[2]

Active Diffusion of Knowledge

In addition to signing licensing deals, Integra has actively promoted the diffusion of knowledge developed from the project's technical accomplishments. Company scientists and other personnel have made numerous industry and academic presentations on the characteristics of the new polymer and on the tests of its mechanical properties and biocompatibility. Two scientists from Integra were invited to speak at an International Symposium on Polymeric Drugs and Drug Delivery Systems in Boston, August 1998, sponsored by the American Chemical Society. Currently, Dr. Kohn and Integra's other personnel have published 15 peer-reviewed articles dealing with this new polymer, including those for the American Chemical Society and the Materials Research Society.

A Platform Technology with Multiple Uses

The new bioabsorbable polymer is a platform technology with the potential to answer many challenging clinical and commercial needs. Integra has begun to adapt the technology, which recently won the Thomas Alvin Edison Award, to new applications including cartilage repair, wound care, cardiovascular repair, and drug delivery.

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2 Telephone interview with Dr. Brode of Integra, Nov. 27, 2000.

This status report was written during 1999-2000 and published in December 2001.